REMARKS

Claims 1, 2, 10, 12-13 and 20-21 are pending in this application, non-elected claims 3-9 and 14-19 being canceled. Reconsideration and allowance are respectfully requested.

Claims 1, 2, 10 and 12-13 have been amended to better conform to preferred U.S. patent practice and to clarify the subject matter of the claims. Claim 11 has been canceled and the subject matter thereof incorporated into amended claim 12. Claim 1 was amended to correct an inadvertent typographical error and to clarify the subject matter recited therein. Support for amended claims can be found throughout the application as originally filed, including the original claims. Specific support for claim 1 can be found at, *inter alia*, pages 1 and 6-7 of the specification. Claim 2 has been amended for clarification purposes, support for which can be found in the examples and in the specification at pages 1 and 6-7 of the specification. Particular support for amended claim 10 can be found in the specification at page 6, line 3 through page 7, line 5; and at page 34, lines 20-28. Specific support for amended claim 12 can be found in the specification at page 5, lines 21-33; and page 7, lines 2-5. New claims 20-21 find support in original claims 1, 2, 10 and 13, as well found in the specification at page 6, line 3 through page 7, line 5; and at page 34, lines 20-28. Applicants respectfully submit that no new matter has been introduced into the application via these amendments to the claims.

Claims 2 and 10-13 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to distinctly claim the subject matter deemed the invention. In particular, the Examiner objected to the recitation of the term "essentially". Applicants traverse this rejection for at least the following reasons.

The word "essentially" opens the claims to the inclusion of subject matter that would not materially affect the basic and novel characteristics of the sequences defined in the claims.

In re Janakirama-Rao, 317 F.2d 951 (C.C.P.A. 1963). The claimed polypeptide having a homologous sequence essentially identical to SEQ ID NOS. 13 and 15 retains the functions of CRAM-1 polypeptides. Thus, any minor modifications in the essentially homologous sequences do not affect the ability of the claimed polypeptides encoded by the essentially homologous sequences with respect to modulating vascular permeability and inhibiting transendothelial migration of leukocytes. Applicants respectfully submit that the amended claims do not recite this term, and that the Section 112(2)-based rejection of the claims should be withdrawn. New claim 20 does recite the phrase "having essentially 100% sequence homology", which Applicants respectfully assert is definite.

Claims 1-2 and 10-13 were rejected under 35 U.S.C. § 112, first paragraph, as lacking an enabling description. The Examiner asserts that a skilled artisan would not expect a polypeptide having anything less than 100% identity over the full length of SEQ ID NO.: 13 or SEQ ID NO.:15 to share the same function as the polypeptide of SEQ ID NO.: 13 or SEQ ID NO.:15 due to unpredictability in the art.

Claims 1-2 and 10-13 were also rejected under 35 U.S.C. § 112, first paragraph, as lacking a sufficient written description to show possession of the claimed invention at the time the invention was made. The Examiner asserts that the variability of homology between all polypeptides embraced by the claims and the polypeptide of SEQ ID NO.: 13 or SEQ ID NO.:15 precludes support in written description of the application.

Applicants traverse these Section 112(1)-based rejections of the claims, asserting that the claims as submitted were adequately supported and enabled by the specification as filed. However, in an attempt to expedite examination on the merits, Applicants have amended claims 1-2, 10 and 12-13 to more clearly describe the invention.

The amended claims are enabled pursuant to the detailed materials and methods of the application. A skilled artisan would be able to make and use the claimed polypeptides according to the disclosure of the application as filed.

The claims are supported by the by the figures and written description at, *inter alia*, pages 5-7, 17-18 and pages 22-28 of the specification. For example, the specification teaches at pages 6-7 that soluble polypeptides having essentially the same amino acid sequences as CRAM polypeptides are functional, capable of targeting the functions of the vascular endothelium. Any mutations or deletion in the amino acid sequences of the claimed isolated polypeptides would necessarily have to be at positions within the sequences that would not eliminate the functional capabilities recited in the claims. A skilled artisan would recognize that Applicants were in possession of the claimed polypeptide at the time the application was filed.

As discussed herein, amended claims 1-2, 10, 12 and 13 are enabled and supported by the written description of the application. Applicants respectfully submit that the Section 112(1)-based rejections should be withdrawn.

Claims 1-2, 10-11 and 13 were rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/06551 to Dumas Milne Edwards (hereinafter WO '551). The Examiner asserts that the cited reference discloses an amino acid sequence that is 100% identical to residues 1-89 of SEQ ID NO.: 15 and exhibits 70% sequence homology with an unidentified portion of SEQ ID NO.: 13. The Examiner also asserts that the polypeptide encoded by SEQ ID NO.: 294 of WO '551 inherently possesses the functional characteristics of the claimed polypeptides. Applicants traverse this rejection for at least the following reasons.

The claimed polypeptides are members of the Immuoglobulin Superfamily of adhesion molecules. Contrary to the Examiner's misleading assertions of record, all of the claimed polypeptides share the functional characteristic of being confluency regulated

adhesion molecules. Portions of the polypeptides constitute immunogenic peptides against which anti-Confluency Regulated Adhesion Molecule (CRAM) antibodies may be targeted.

By contrast, WO '551 discloses 5'ESTs derived from soluble or receptor proteins. SEQ ID NO.: 294 of WO '551 sets forth an amino acid sequence 89 residues in length. This EST was cited by the Examiner as inherently possessing the function of the claimed adhesion molecule members of the Immunoglobulin Superfamily. The Examiner offers no support for this notion. In fact, no particular function is assigned to SEQ ID NO.:294 by the authors of WO '551. No teaching of WO '551 would lead a skilled artisan to believe that the peptide encoded by the 89 amino acids of SEQ ID NO.: 294 would constitute an adhesion molecule member of the Immunoglobulin Superfamily. Thus, the cited EST of WO '551 does not anticipate the claimed CRAM polypeptides. Applicants respectfully submit that this Section 102-based rejection should be withdrawn.

The Examiner has objected to the informal drawings submitted with the application upon filing. Applicants are in the process of preparing formal drawings, which will be submitted in a Supplemental Response.

The Examiner also noted that a certified copy of the priority document has not been received by the Patent Office. Applicants will submit the certified copy of the priority document upon receipt in a Supplemental Response.

Applicants included herewith a substitute Sequence Listing in both paper and electronic format, pursuant to 37 C.F.R. §§ 1.821-1.825. Applicants respectfully submit that the substitute Sequence Listing does not introduce new matter into the pending application, and that the contents of the paper and electronic versions of the Sequence Listing are the same. Entry of the substitute Sequence Listing is requested.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the application is in condition for allowance. Notification to that effect is earnestly

solicited. Should any questions related to patentability remain, the Examiner is invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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TAC/amx
Enclosure: Appendix

APPENDIX
MARK UP VERSION SHOWING CHANGES MADE

IN THE SPECIFICATION:

Paragraphs of the specification have been amended as indicated below.

At page 3, beginning at line 5:

Based on this finding the invention provides a method for the specific identification of differentially expressed DNA-sequences comprising the use of Differential Display Reverse Transcription PCR, in which one set of partially or completely degenerated primers specific for the target gene is used. One major limitation of the conventional RNA display strategy is the lack of specificity of the method. In the aim to increase this specificity, the inventors in their search for other adhesion molecules used degenerated primers targeting the sequence encoding molecules with C_2 domains. The was achieved by the alignment of C_2 domains of several Ig Sf adhesion molecules, and the identification of a linear amino-acid consensus, surrounding the cysteine residue participating to the C_2 domain structure: Y-(RQYS)-C-x-A-S-N-x_2-G (SEQ ID NO.: 22). In a more general sense, this approach can also be used in the search for other sequences in which the reverse translation of one or more of the most frequent consensus sequences is used to design the degenerated primers used for differential display.

At page 5, beginning at line 21:

In addition to using the sequence information of the two CRAM proteins disclosed herein for identifying other members of the family in other species, like humans, the two proteins and their corresponding family members can also be used for the preparation of

derived molecules, such as antibodies directed against the (poly)peptides of the invention, or recombinant equivalents of the proteins, optionally in soluble form, or peptides comprising at least part of the amino acid sequence of the polypeptides. Suitable parts of the amino acid sequence are especially the extracellular domains: VC_2, and the membrane proximal cytoplasmic sequence: A-[Y,Q]-[R,S]-[R,K]-G-[C,Y]-F (amino acids 266-272 of SEQ ID NO.:13 or amino acids 261-267 of SEQ ID NO.: 14).

At page 9, beginning at line 5:

Fig 8: (A) nucleotide and deduced amino acid sequence of the Confluency Regulated Adhesion Molecule 1 (CRAM-1) cDNA. The putative hydrophobic signal peptide (first) and transmembrane region (second) are underlined. Predicted N-glycosylation sites (strikeout), cysteines likely to form disulfide bonds (brackets) and Ser/Thr/Tyr residues of possible phosphorylation sites (bold) are indicated. (B) Structural model for murine CRAM-1 protein. Extracellular part showing a VH and a C2 like Ig domain with two putative N-linked glycosylation sites. The arrow points to the region targeted by the partially degenerated primers (YYCXAS1) (SEQ ID NO.:20) used in the Targeted Differential Display.

At page 22, beginning at line 2:

The regulation of genes in endothelial cells depends on their environment. The present invention was directed to the identification of genes that undergo regulation upon the contact of endothelium with tumor cells. For this purpose, an in vitro assay was developed using the co-culture of melanoma tumor cells (B16) with an endothelioma cell line (t-end). Total RNA extracted from the mix was used as a template to prepare cDNA submitted to a differential PCR screen. The cDNA obtained from the endothelial or melanoma cells cultured on their own were used as controls. The three different patterns were compared to

identify the transcripts regulated by the co-culture condition. To limit the analysis to the sequences encoding for cell surface molecules of Ig superfamily, partially degenerated primers were used that target the sequence surrounding the C-terminal cysteine of C2 domains in Ig superfamily molecules. The most reproducible pattern of PCR products was obtained using primers that encode the sequence YYCxAS1 (Fig 7A, SEQ ID NO.: 20). This improved method of RNA display technique was named TDD for "Targeted Differential Display".

At page 33, beginning at line 11:

The new screening strategy, named Targeted Differential Display (TDD), has proved to be an efficient technique in selectively amplifying cDNA of interest. TDD successfully exploited the use of partially degenerated primers to confer selective targeting to the conserved region, Y(Y/Q/R)CXAS (SEQ ID NOs.: 18-20), of C2 like Ig domains. Repeated experiments lead to reproducible display patterns. Out of 16 differentially expressed transcripts, three correspond to genes with significant homology to conserved Ig sequences. This increase in specificity manages to overcome the major difficulties in the already known techniques of classical RNA fingerprinting and differential display. RNA fingerprinting has long been used for the identification of differentially expressed genes. However, due to the sequence specific primers employed, this method detects only the transcripts of selected and already known proteins. On the other hand, RNA display employs random primers and involves the non-specific amplification of transcripts. The aim in this case is to pinpoint any differences in mRNA levels between two biological systems, which are submitted to comparison. TDD is an advanced screening method that combines the specificity of RNA fingerprinting with the degeneracy of Differential RNA Display resulting in selectivity. Due to the targeting of related transcripts, this technique significantly reduced the time needed for

screening. The identification of new members of specific protein families, therefore, becomes possible. This is a

IN THE CLAIMS:

The claims have been amended as indicated below.

1. (Twice Amended) An isolated [isoalted] polypeptide belonging to a subfamily of the [human] Immunoglobulin Superfamily [, which polypeptide shows at least 70% sequence homology with] consisting essentially of all or part of the amino acid sequence of [the] murine Confluency Regulated Adhesion Molecule 1 (muCRAM-1, SEQ ID NO: 13) [or CRAM-2 (SEQ ID NO.: 14)], the isolated polypeptide being capable of modulating vascular endothelium function.

2. (Twice Amended) An isolated [The] polypeptide [as claimed in claim 1] belonging to a subfamily of the Immunoglobulin Superfamily [comprising an amino acid sequence that is 70% to essentially 100% homologous to] consisting essentially of all or part of the amino acid sequence of human Confluency Regulated Adhesion Molecule 1 (huCRAM-1 [(] SEQ ID NO.: 15) , the isolated polypeptide being capable of modulating vascular endothelium function.

10. (Amended) The isolated polypeptide according to claim 13, wherein the [Soluble] polypeptide [having essentially the same amino acid sequence as the polypeptide as claimed in claims 1 and 2 for use in the treatment of inflammation reactions] is a soluble polypeptide that inhibits transendothelial migration of leukocytes.

12. (Twice Amended) The isolated [The] polypeptide according to claim 10, [as claimed in claim 11, wherein] the polypeptide comprising at least [part of the amino acid sequence] one sequence against which anti-CRAM antibodies can be directed, [comprises] the at least one sequence being selected from the group consisting of [the] extracellular domain V, extracellular domain C_2 [domains VC2,] and the membrane proximal cytoplasmic sequence defined by amino acids 266-272 of SEQ ID NO.: 13 [or amino acids 261-267 of SEQ ID NO.: 14].

13. The isolated polypeptide as claimed in claims 1, or 2 in soluble form [for use in modulating vascular permeability].